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Circadian disruption, shift work and the risk of cancer: a summary of the evidence and studies in Seattle

Scott Davis · Dana K. Mirick

Abstract There is increasing interest in the possibility that disruption of normal circadian rhythm may increase the risk of developing cancer. Persons who engage in nightshift work may exhibit altered nighttime melatonin levels and reproductive hormone profiles that could increase the risk of hormone-related diseases, including breast cancer. Epidemiologic studies are now beginning to emerge suggesting that women who work at night, and who experience sleep deprivation, circadian disruption, and exposure to light-at-night are at an increased risk of breast cancer, and possibly colorectal cancer as well. Several studies have been conducted in Seattle recently to investigate the effects of factors that can disrupt circadian rhythm and alter normal nocturnal production of melatonin and reproductive hormones of relevance to breast cancer etiology. Studies completed to date have found: (1) an increased risk of breast cancer associated with indicators of exposure to light-at-night and night shift work; and (2) decreased nocturnal urinary levels of 6-sulphatoxymelatonin associated with exposure to 60-Hz magnetic fields in the bedroom the same night, and a number of other factors including hours of daylight, season, alcohol consumption and body mass index. Recently completed is an experimental crossover study designed to investigate whether exposure to a 60-Hz magnetic field under controlled conditions in the home sleeping environment is associated with a decrease in nocturnal urinary concentration of 6-sulphatoxymelatonin, and an increase in the urinary concentration of luteinizing hormone, follicle stimulating hormone, and estradiol in a sample of healthy women of reproductive age. Presently underway is a study to determine whether working at night is associated with decreased levels of urinary 6-sulphatoxymelatonin, and increased urinary concentrations of the reproductive hormones listed above in a sample of healthy women of reproductive age, and to elucidate characteristics of sleep among night shift workers that are related to the hormone patterns identified. A proposal is under review to extend these studies to a sample of healthy men to investigate whether working at night is associated with decreased levels of urinary 6-sulphatoxymelatonin, and increased concentrations of urinary cortisol and cortisone, urinary levels of a number of androgen metabolites, and serum concentrations of a number of reproductive hormones. Secondarily, the proposed study will elucidate characteristics of sleep among night shift workers that are related to the hormone patterns identified, as well as investigate whether polymorphisms of the genes thought to regulate the human circadian clock are associated with the ability to adapt to night shift work. It is anticipated that collectively these studies will enhance our understanding of the role of circadian disruption in the etiology of cancer.

Keywords Breast cancer · Circadian rhythm · Electromagnetic fields · Environmental carcinogens · Light · Melatonin · Pineal · Shift work

S. Davis (✉)
Program in Epidemiology, Division of Public Health Sciences Fred Hutchinson Cancer Research Center and Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, 1100 Fairview Avenue North M4-B874, P.O. Box 19024, Seattle, WA 98109-1024, USA
e-mail: sdavis@fhcrc.org
Tel.: +1-206-667-2750
Fax: +1-206-667-4787

D. K. Mirick · S. Davis
Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

There is increasing interest in the possible role of environmental factors that can alter normal endocrine function, often referred to as 'endocrine disruptors,' in the etiology of cancer. Of particular interest is the potential influence of exposure to light-at-night, and sleep disruption, on endocrine function and the regulation of hormones that are important in the etiology of some types of cancer. Persons who engage in night shift work are subject to the influence of both factors, and may exhibit altered hormone profiles as a result that could increase the risk of hormone-related diseases, including breast and prostate cancer.

There is now considerable evidence that night shift workers experience a variety of physical symptoms and adverse health effects. Most notable are those associated with gastrointestinal dysfunction [1–3], cardiovascular morbidity [4–10], and some aspects of reproductive health. Specifically, night shift workers have been reported to be at increased risk of adverse pregnancy outcomes such as preterm births and low birth weight [11–16], spontaneous abortion [17–21], and reduced fecundity [21–23].

A number of studies have investigated a potential link between night shift work and cancer. Four studies have directly investigated the association between night shift work and the development of breast [24–26] and colon [27] cancer. Hansen [24] reported an increased risk of breast cancer associated with occupational shift work exposure (primarily women working in catering jobs or as air cabin attendants) in a large study (over 6000 cases) in Denmark. Davis et al. have reported an increased risk of breast cancer in women who engaged in graveyard shift work [25], and Schernhammer et al. [26] reported similar results in nurses who worked rotating shifts. More recently, Schernhammer et al. have extended their work to consider the effect of night shift work on the risk of other cancers. They found an increased risk of colorectal cancer associated with working rotating night shifts among female participants in the Nurses' Health Study [27]. More indirectly, increased risks of breast cancer have been reported among flight attendants [28, 29] and shift-working Norwegian radio and telegraph operators working at sea [30]. Numerous studies have found an increased risk of prostate cancer among airline pilots [31–38]. Excess prostate cancer has also been reported in firefighters [34, 39, 40], health practitioners and physicians [34, 40], and police and law enforcement personnel [34, 40], all of which are occupations which typically require some degree of night shift work. Collectively these findings provide intriguing evidence that suggests working at night, or in occupations characterized by night shift work, may be associated with an increased risk of cancer. Additional studies are now needed to better define what aspects of night shift work (if any) are responsible for the increased risks observed.

Key in the regulation of the circadian clock is the pineal gland, which provides a hormonal signal synchronized to the daily light–dark cycle. Melatonin appears to be involved in the regulation of gonadal function by influencing the hypothalamic-pituitary-gonadal axis. Decreased concentrations of circulating melatonin (such as those brought about by circadian disruption) can result in increased release of gonadotropins from the pituitary, thereby stimulating testicular testosterone or ovarian estrogen production and release. Conversely, melatonin secretion appears to be unaffected by fluctuations in gonadal steroids. Thus, through its control over gonadal hormone production, melatonin may have an inhibitory effect on hormone-dependent tumors. Melatonin may also have a more direct effect on the development of cancer. Growth-inhibitory and oncostatic properties of melatonin have been well described. A number of in vitro studies have reported a reduction in the growth of malignant cells and/or tumors of the breast [41–45] prostate [46–51], and other tumor sites [52–56] by both pharmacological and physiologic doses of melatonin. In rodent models, pinealectomy has been found to enhance tumor growth [57], and exogenous melatonin administration has demonstrated anti-initiating [58] and oncostatic activity [59–62] in various chemically induced cancers as well as in virus transmitted tumors in mice [63]. A number of mechanisms have been proposed to explain such direct anti-cancer activity: melatonin may have antimitotic activity by its direct effect on hormone-dependent proliferation through interaction with nuclear receptors; it may affect cell-cycle control; and it may increase the expression of the tumor-suppressor gene p53.

Light exposure has also been investigated directly in relation to cancer development in experimental animals. In 1964, Jöchle reported that spontaneous mammary tumors in C3H-A mice increased with constant illumination [64]. Later, Shah et al. [65] reported that constant light increased DMBA-induced mammary tumorigenesis in rats. Animals exposed to constant light also showed greater DNA synthesis activity in the mammary tissue, and higher levels of circulating prolactin. Experimental evidence suggests that light exposure during the dark cycle increases the progression of cancer [66, 67], and that dim light is as effective in this regard as bright and constant light [68, 69].

Epidemiologic studies of exposure to light-at-night in relation to cancer risk are exceedingly difficult to conduct. One approach has been to investigate whether profoundly blind women, who generally do not perceive light, are at a reduced risk of breast cancer. Using more than 100,000 U.S. hospital discharge records, Hahn identified women with a primary diagnosis of breast cancer and a comparison group of women with stroke or cardiovascular disease. Among the comparison group, 0.26% were found profoundly blind, whereas among the women with breast

cancer, only 0.15% were profoundly blind [70]. Feychting et al. [71] reported similar findings based on a cohort study in Sweden. Pukkala et al. [72] also found lower breast cancer risk in blind women in Finland although risk for other cancers was higher, in contrast to the Swedish study. In an extension of the study in Finland for an additional year, Verkasalo et al. [73] included additional breast cancer cases and further refined the definition of visual impairment to include five categories from moderate low vision to total blindness. The Standardized Incidence Ratio declined from 1.05 in women with 'moderate low vision' to 0.47 in totally blind women; the decrease was monotonic and statistically significant. A recent report from Norway [74] also suggests a lower risk in blind women. Two of the studies described above also reported results regarding prostate cancer in men. Feychting et al. found reduced prostate cancer incidence among profoundly blind men, but not among those classified as visually impaired but not blind [71]. Although prostate cancer risk was not reduced among partially sighted or almost blind men in the study conducted by Pukkala et al., there were no cases of prostate cancer among blind men [72].

A number of genes have now been identified that are believed to be important in the regulation of circadian rhythms [75]. The *Period* (*Per*) gene family is central to this mechanism, as is the *h*CLOCK gene. Recently, specific polymorphisms in these genes have been found to be associated with a number of sleep-related conditions, including diurnal preference (*h*CLOCK, [76]; *Per3*, [77]); delayed sleep phase syndrome and extreme diurnal preference (*Per3*, [78], [79]); and insomnia in mood disorders (*h*CLOCK, [80]). Of particular interest is new evidence that a polymorphism of *Per3* is associated with the development of breast cancer [81], and an alteration in *Per2* has been shown to affect tumor suppression and DNA damage response in mice [82]. Thus, it is likely that there is a genetic component that affects an individual's ability to adapt to circadian disruption, for example as a result of working at night. If so, specific genotypes may define groups that are more or less susceptible to the effects of working night shifts, including the effects on melatonin and reproductive hormones, and consequently the risk of developing hormone-related cancer such as prostate or breast cancer.

Several studies have been conducted in Seattle to investigate the effects of factors that can disrupt circadian rhythm and alter normal nocturnal production of melatonin and reproductive hormones of relevance to breast cancer etiology. The first study was a population-based case–control study of breast cancer, designed to determine whether exposure to light-at-night and/or residential power frequency magnetic fields increases the risk of breast cancer in women [25]. Cases of breast cancer (n=813), aged 20–74 years, were diagnosed from November 1992 through March 1995. Controls (n=793) were identified by random-digit dialing and were frequency matched to cases according to 5-year age groups. An in-person interview was used to gather information on sleep habits and bedroom lighting environment in the 10 years before diagnosis, and a lifetime occupational history. In summary, findings indicated that: (1) Breast cancer risk was increased among subjects who frequently did not sleep during the period of the night when melatonin levels are typically at their highest, defined as between 1:00 and 2:00 am in this study (OR=1.14 for each night per week, 95% C.I=1.01–1.28); (2) Breast cancer risk was increased with increasing number of years (in the 10 prior to reference date) of having a sleep pattern in which the subject frequently (3 or more nights/week) did not sleep during the period of the night when melatonin levels are typically highest, with the category of longest exposure (4.6 years or more) having a greater than two-fold increase in risk (OR=2.3, 95% C.I=1.2–4.2); and (3) Ever having worked graveyard shift was associated with an increased breast cancer risk (OR=1.6, 95% C.I.=1.0–2.5), with a trend of increasing risk with increasing years and with more hours per week of graveyard shift-work (P_{trend}=0.02, Wald χ^2).

The second study was undertaken to address the more fundamental question of whether one specific factor thought to disrupt circadian rhythms, 60-Hz magnetic fields, can suppress the normal nocturnal rise in melatonin. This study [83] investigated whether such exposure was associated with lower nocturnal urinary concentration of 6-sulfatoxymelatonin in 203 women aged 20–74 years with no history of breast cancer. Each woman was interviewed and provided data on the following for a 72-h period at two different seasons of the year: (1) Magnetic field and ambient light measured every 30 s in her bedroom, (2) Personal magnetic field measured at 30-s intervals, and (3) Complete nighttime urine samples for three consecutive nights. Lower nocturnal urinary 6-sulfatoxymelatonin level was associated with more hours of daylight, older age, higher body mass index, current alcohol consumption, and current use of medications classified as beta blockers, calcium channel blockers, or psychotropics. After adjustment for these factors, higher bedroom magnetic field level was associated with significantly lower urinary concentration of 6-sulfatoxymelatonin during the same night, primarily in women who used these medications and during times of the year with the fewest hours of darkness. These principal findings provide some of the first population-based evidence that a factor thought to affect normal pineal function is associated with a reduction in the normal nocturnal rise in melatonin levels in humans. Results were also internally consistent regarding the effects of a number of factors previously shown to affect pineal function, and

demonstrated that the field methods and assay employed were capable of detecting changes in hormone levels of the type predicted.

The third study investigated whether exposure to magnetic fields under controlled conditions in the home sleeping environment is associated with a decrease in nocturnal melatonin levels and an increase in urinary concentrations of estradiol, luteinizing hormone (LH), and follicle stimulating hormone (FSH) in healthypre-menopausal women. A secondary aim was to characterize the relationship between nocturnal levels of melatonin and estradiol, LH, and FSH. The study recruited approximately 160 participants and employed a cross-over design, with stringent eligibility criteria to ensure participants exhibited normal ovarian function and had predictably regular menstrual cycles. Menstrual cycle regularity was evaluated in month 1 of the study using an ovulation prediction kit. Upon ovulation in month 2, half of the subjects were assigned to sleep with a small, common household appliance, which emitted a steady, measurable magnetic field underneath the bed beginning day 1 post-ovulation, for five consecutive nights. During the last night of exposure, the subject collected all urine excreted during the night, including the first void the next morning. Procedures in month 3 were the same, except the subject slept with the appliance turned off. The other half of the subjects were assigned the reverse order of exposure assessment. Magnetic field levels at the head of the subject's bed were recorded during the 5 days of exposure/non-exposure period. Subjects were blinded to the on/off status of the appliance.

To date, a preliminary analysis has investigated whether nocturnal urinary melatonin levels are lower under exposure conditions relative to non-exposure. Analyses were conducted with no adjustment for covariate factors, and with adjustment for the following factors shown in the melatonin study described above to be associated with nocturnal melatonin levels: age, hours of darkness (a measure of season), alcohol consumption in the previous 24 h, body mass index, and use of medications classified as psychotropics in the previous 24 h. Using standard analytical methods for analyzing cross-over data, there was no evidence of a carry-over effect of exposure or a period effect; therefore, these effects were not considered further. Preliminary findings indicate that nocturnal 6-sulphatoxymelatonin level was lower in the exposure month, relative to the non-exposure month, but this was not statistically significant. After adjustment for the factors listed above, the effect of exposure on 6-sulphatoxymelatonin levels was slightly more pronounced and statistically significant. These results provide important preliminary evidence that exposure to 60-Hz magnetic fields decreases the normal nocturnal rise in melatonin, and constitutes the first evidence of this type in a population setting under largely controlled conditions. Analyses are underway regarding the effects of the exposure on the reproductive hormones.

The fourth study, which is currently ongoing, was designed to directly pursue evidence that suggests night shift work may increase cancer risk, and breast cancer risk in particular. This study will investigate whether working at night is associated with decreased levels of the urinary concentration of 6-sulphatoxymelatonin, and increased levels of reproductive hormones believed to be directly related to the development of breast cancer, in a sample of healthy women of reproductive age. Secondarily, the study will investigate whether urinary levels of melatonin are lower and levels of reproductive hormones are higher during daytime sleep relative to nighttime sleep among women who work at night. Approximately 200 women healthcare professionals between the ages of 22 and 45 who work the night shift and 150 who work the day shift exclusively are being recruited in the Seattle metropolitan area. Stringent eligibility criteria are in place to ensure participants exhibit normal ovarian function and predictably regular menstrual cycles, and that they not be taking hormone contraceptives and not have been pregnant or breast feeding in the last year. In addition, the night shift women must normally sleep at night during off days. This study allows for both between-subject comparisons of night shift versus day shift workers, and within-subject comparisons during day sleep versus night sleep among the night shift workers. In the first month of the study menstrual cycle regularity is evaluated, the day of ovulation is determined using a commercial kit, a personal interview regarding employment, reproductive history, and assessment of adaptability to shift work is conducted, and a blood sample is collected. In the second month urine sample collections are scheduled during both work and sleep periods, taking place in the early to mid-luteal phase of each participant's cycle. Sleep patterns are measured *via* actigraphy during the sleep periods corresponding to urine collection, and oral temperature data are collected during wake-time in the night shift workers to determine temperature amplitude. Information is also collected on factors which may be related to the hormones under study, such as alcohol consumption, medication use, and hours of daylight. Urine samples will be assayed for 6-sulphatoxymelatonin and levels of LH, FSH, and estrogen.

This study will test the following hypotheses between graveyard and day shift workers: (1) urinary 6-sulphatoxymelatonin levels are *lower* and urinary levels of estrogen and the gonadotropins LH and FSH are *higher* in graveyard shift-working women during daytime sleep than in day shift-working women during nighttime sleep;

(2) nocturnal urinary 6-sulphatoxymelatonin levels are *lower* and nocturnal urinary levels of estrogen and the gonadotropins LH and FSH are *higher* in graveyard shift-working women during nighttime sleep on off-nights than in day shift-working women who always sleep at night; (3) women who work during the day and sleep at night get *more* hours of sleep, have *higher* sleep efficiency, and *fewer* number of arousals after sleep onset than those who work the graveyard shift and sleep during the day; and (4) women who work during the day and sleep at night report having *higher* sleep quality than those who work the graveyard shift and sleep during the day. The study will test the following hypotheses among graveyard shift workers: (1) urinary 6-sulphatoxymelatonin levels are *lower* during daytime sleep than during nighttime sleep; (2) urinary levels of estrogen and the gonadotropins LH and FSH are *higher* during daytime sleep than during nighttime sleep; (3) individuals who score highly on measures of ability to adjust to shift work get *more* hours of sleep, have *higher* sleep efficiency, and *fewer* number of arousals after sleep onset during daytime sleep than those with lower adjustability scores; (4) individuals who score highly on measures of ability to adjust to shift work have *higher* urinary 6-sulphatoxymelatonin levels during daytime sleep than those with lower adjustability scores; and (5) individuals who have higher temperature amplitudes (an indicator of adaptation to shift work) have *higher* urinary 6-sulphatoxymelatonin levels during daytime sleep than those with lower temperature amplitudes.

Finally, a proposal is under review to extend these studies to a sample of healthy men. The primary objective of the proposed study is to determine whether working at night is associated with: (1) decreased levels of the urinary concentration of 6-sulphatoxymelatonin; (2) increased concentrations of testosterone, dihydrotesterone (DHT), 3-α androstanediol glucuronide (AAG), dehydroepiandrosterone sulfate (DHEAS), estrone, and estradiol in serum; (3) increased urinary concentrations of the following androgen metabolites: conjugated testosterone, DHT, etiocholanolone, androsterone, androstanediol, and DHEA; (4) and decreased serum levels of sex hormone-binding globulin (SHBG). Secondarily, this study is designed to investigate: (1) whether urinary levels of melatonin are lower and serum and urinary levels of the androgens and metabolites listed above are higher during daytime sleep relative to nighttime sleep among men who work at night; and (2) if certain polymorphisms of the human circadian clock genes are associated with an individual's ability to adapt to night shift work. Approximately 200 male health care workers who work the night shift and 150 male health care workers who work the day shift will be recruited as volunteers in the Seattle metropolitan area. Eligible participants must be between the ages of 22 and 55, employed for at least 20 h/week, do not take hormone preparations, and have no personal history of prostate cancer. In addition, the night shift workers must normally sleep at night during off days. Participation includes completion of an in-person interview, assessment of ability to adapt to shift work, and blood and urine collections that will be scheduled during both work and sleep periods. Sleep patterns will be measured *via* actigraphy during the sleep periods corresponding to sample collection. Oral temperature data will be collected during wake-time in the night shift workers to determine temperature amplitude. Information will be collected on factors which may be related to the hormones under study, such as alcohol consumption, medication use, and hours of daylight during sample collection. Serum and urine samples will be assayed for the hormones listed above, and blood samples will be genotyped for specific polymorphisms of the *h*CLOCK, *Per2*, and *Per3* genes.

In summary, findings from studies conducted in Seattle have found that exposure to light-at-night and working at night (graveyard shift) are associated with an increased risk of breast cancer. Exposure to power frequency magnetic fields reduces nocturnal melatonin levels in healthy women of reproductive age, as does increasing hours of daylight. Analyses are currently underway evaluating whether exposure to magnetic fields under controlled conditions not only reduces nocturnal melatonin levels, but also increases urinary levels of estrogen, LH and FSH; hormones of relevance to the etiology of breast cancer. An ongoing study is currently investigating the impact of working night shifts on melatonin and female reproductive hormone levels, and will have the capability of evaluating the role of variations in genes involved in the regulation of the human circadian clock on a person's ability to adapt to shift work. Efforts are underway to expand these studies of the effects of night shift work on melatonin and reproductive hormones, and the role of genetic variation in a person's ability to adapt to shift work, to include men.

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